REMARKS

The Amendments

The claims are amended to remove the "hydrate" and "solvate" terms except for the "hydrate" term being retained as an option for the tiotropium salt. The amendment addresses the 35 U.S.C. §112 rejection as discussed below.

Applicants reserve the right to file one or more continuing and/or divisional applications directed to any subject matter disclosed in the application which has been canceled by any of the above amendments.

The Rejection under 35 U.S.C. §112, first paragraph

The rejection of claims 1, 3, 4, 9, 10, 15-17, 19-21, 23, 25, 26, 31-37, 39 and 63-66 under 35 U.S.C. §112, first paragraph, for alleged lack of enablement, is respectfully traversed.

The rejection is made based on the allegation that the specification does not enable one of ordinary skill in the art to make and use the solvates or hydrates (hydrate being a solvate where the solvent is water) of the compounds as claimed. The rejection is, therefore, rendered moot, at least in part, by the above amendments. The solvate and hydrate recitations have been removed from the claims except for the hydrate term still being maintained specifically for the tiotropium salt component.

Applicants maintain their previous arguments to support that hydrates of tiotropium salts are enabled. Thus, arguments are particularly strengthened in view of the current claims. The instant specification specifically exemplifies preparation of a hydrate of tiotropium salt at page 20, lines 5-22. Thus, the allegations in the Office action that the specification does not provide any teaching or guidance as to making the claimed hydrates are incorrect. The Wands factors regarding the amount of direction provided, the existence of working examples and the quantity of experimentation needed are thus all clearly in applicants' favor as to the current claims. The level of skill in the art and breadth of claims factors also clearly favor applicants' position. As to the state of the prior art and predictability factors, the PTO has provided some evidence to support their position but the applicants have also provided good evidence to support their position. As a whole, applicants again urge that the Wands factors

favor a finding of enablement for the current claims.

Applicants further disagree on the position taken in the Office action regarding predictability. It is not necessary for one of ordinary skill in the art to be able to predict – before conducting the experimentation – the outcome of their routine experimentation in order to support enablement. One of ordinary skill in the art conduct routine experimentation to provide the solvates and hydrates of the claimed compounds which would be useful for carrying out the invention. The legal requirement to include consideration of routine experimentation would be completely eviscerated if the law required one of ordinary skill in the art to be able to predict the outcome before the experimentation was conducted. When the correct standard is applied, there is adequate enablement for one of ordinary skill in the art to make and use the hydrates of the tiotropium salts as currently claimed.

For the above reasons, the rejection under 35 U.S.C. §112, first paragraph, for lack of enablement should be withdrawn.

The Provisional Obviousness-type Double Patenting Rejections

The provisional obviousness-type double patenting rejection over copending application no: 11/424,244 is respectfully traversed.

Applicants maintain their previous position that the instantly claimed subject matter is patentably distinct from the subject matter claimed in the copending application. The instant claims are directed to a very specific combination of a tiotropium compound, a ciclesonide steroid compound and a particular type of excipient. None of the claims in the copending application are directed to such a specific combination of components. The copending application only contains two claims (i.e., claims 71 and 72) directed to compositions and the rejection can only be based on the claims of the application. Although these copending claims contain comprising language which leaves their interpretation open to other components, these claims do not recite the inclusion of ciclesonide or the specific excipient recited for the currently claimed invention. The possibility of arriving at compositions meeting the claimed requirements from such broad copending claims is far too remote to be considered establishing patentable indistinctness. None of the copending claims provide any suggest to the specific combination of a tiotropium compound, a ciclesonide compound and the particular excipient of the instant claims. In view of the distinction in the claimed subject

matter, the provisional rejections should be withdrawn.

Additionally, applicants submit that the provisional rejection should be withdrawn because the copending application was filed after the effective US filing of the instant application. Based on its parent filing date, the instant application is the first filed application. In accordance with MPEP §804(I)(B)(1) "the examiner should withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer. A terminal disclaimer must be required in the later-filed application before the ODP rejection can be withdrawn and the application permitted to issue." Since all the other rejections are believed to be overcome, the provisional obviousness-type double patenting rejection based on this later-filed applications should be withdrawn.

The First Rejection under 35 U.S.C. §103

The rejection of claims 1, 3, 4, 9, 10, 15-17, 19-21, 23, 25, 26, 31-37, 39 and 63-66 under 35 U.S.C. §103, as being obvious over the combination of Nishimura (Allergology) and Banholzer (U.S. Patent No. 5,610,163), is respectfully traversed.

Applicants maintain their previous position that the combined reference teachings fail to create a prima facie case for obviousness of the claimed invention. However, applicants are submitting herewith a Declaration under 37 C.F.R. §1.132 providing further proof of the nonobviousness of the claimed invention.

The data provided in the Declaration provides a clear and convincing showing of significant unexpected advantages for applicants' particular combination. The data show that the combination of tiotropium and ciclesonide provides a surprising and synergistic advantageous benefit in bronchoprotective activity. Treatment with the combination of these specific actives gave a bronchoprotective effect significantly more than the sum of the activities achieved with each separately. Ciclesonide applied at 0.1 mg/kg only induced slight bronchoprotection of about 5% ± 10 %, 3 hours after drug inhalation which remained constant over 24 hours. Tiotropium bromide displayed a dose-dependent bronchoprotection which reached 35% ± 25 % at 0.06 µg/kg, 3 hours after inhalation. The compound retained at the end of the study a bronchoprotection of 12% ± 7 %. The combination of ciclesonide (0.1 mg/kg) and tiotropium bromide (0.06 µg/kg) resulted in an unexpected super-additive

bronchoprotection of 49% ± 7 % at 3 hours and of 41% ± 14 % after 24 hours. The combined administration of tiotropium bromide and ciclesonide resulted in a clearly synergistic bronchoprotection in this model. In particular the effect of the combination was significantly higher than the sum of the values of the respective mono-therapies. Such synergistic effect could not have been expected from the cited prior art. Certainly, the references fail to provide any suggestion of the advantage of applicants' particular combination since neither of the references provide any suggestion to use ciclesonide, particularly, together with a tiotropium compound. Further, even for the combination of a different anticholinergic and steroid in Nishimura, there is no suggestion of synergistic effect. The data of unexpected, synergistic advantages, thus, provides further support for the nonobviousness of the claimed invention. If the references established a prima facie case of obviousness, this proof of nonobviousness would overcome the prima facie case. Thus, it provides an independent basis for withdrawal of the rejection.

It is alleged in the Office action that applicants' previous data was not submitted in declaration form. It is now being submitted in declaration form and should be fully considered.

It is further alleged in the Office action that applicants have not provided a comparison of the claimed composition with any combination of a corticosteroid and an anticholinergic agent. In response, applicants urge that there is more than one way that nonobviousness can be demonstrated by data and that evidence submitted as a showing of nonobviousness must be considered. The PTO's own manual, at MPEP §716.02(a)(I), makes clear that a showing of synergism can be sufficient proof of nonobviousness, stating:

> Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989).

It is not necessary for applicants to provide a comparison to the oxitropium/beclamethasone combination shown by Nishimura because their showing of the synergistic effect of their combination already provides a clear and convincing showing of unexpected properties of the

claimed invention. There are no teachings in the prior art from which one of ordinary skill in the art would have an expectation that the combination of tiotropium and ciclesonide could provide an effect significantly greater than their additive effect. The teachings of Nishimura regarding the oxitropium/beclamethasone combination certainly provide no such expectation. To the contrary, Nishimura itself indicates that the addition of the oxitropium to beclamethasone provided only a "small improvement" in treatment; see the concluding discussion on pg. 87. None of the cited prior art references give any suggestion that a combination of an anticholinergic and a corticosteroid would be expected to result in a synergistic advantageous property.

Considering the record as a whole, applicants urge that they have provided clear and convincing evidence of significant unexpected advantages of their particular combination. The prior art gives no hint to one of ordinary skill in the art that the specific combination of the specific anticholinergic, tiotropium salt, and the specific corticosteroid, ciclesonide, would be particularly advantageous. Thus, a clear and convincing showing of nonobviousness is provided.

Further, applicants submit that the references fail to establish a prima facie case of obviousness or, at most, only a weak case which is readily overcome by the Declaration, for the following reasons.

Nishimura discloses the use of a combination of oxitropium bromide with a certain inhaled corticosteroid, i.e., beclomethasone diproprionate, for use in treating chronic asthma. Nishimura suggests that the combination of the oxitropium bromide provided advantages over beclomethasone diproprionate alone.

Banholzer discloses a generic formula (I) encompassing a range of compounds which includes tiotropium salts. Claim 5 is directed particularly to tiotropium salts.

The basis for the rejection is that it would have been obvious to one of ordinary skill in the art to exchange the oxitropium bromide of Nishimura with the tiotropium compound disclosed in Banholzer. However, such a combination would not meet or suggest the elements of the claims and, thus, not support a prima facie case of obviousness.

The instant claims recite a combination of the tiotropium compound and the particular steroid, ciclesonide. Neither of the references provide any suggestion to combine the particular steroid ciclesonide. Nishimura discloses only a beclomethasone salt and Banholzer

provides no teachings regarding any steroid. The combined reference teachings thus fail to meet this claim element.

The instant claims further recite, in addition to the tiotropium compound and the ciclesonide compound, "a pharmaceutically acceptable excipient selected from the group consisting of glucose, arabinose, lactose, saccharose, and maltose." Neither of Nishimura or Banholzer provide any teaching regarding a composition containing such a particular excipient. Further, the Office action provides no reasoning as to why a composition including this element would be obvious to one of ordinary skill in the art. For this additional reason, therefore, the combined references fail to meet the claim recitations.

For all of the above reasons, it is urged that the cited prior art, considered as a whole on the record, fails to render the claimed invention obvious to one of ordinary skill in the art. Thus, the rejection under 35 U.S.C. §103 should be withdrawn.

The Second Rejection under 35 U.S.C. §103

The rejection of claims 1, 3, 4, 9, 10, 15-17, 19-21, 23, 25, 26, 31-37, 39 and 63-66 under 35 U.S.C. §103, as being obvious over Keller (WO 00/28979, corresp. to U.S. Patent No. 6,645,466), Nishimura (Allergology) and Banholzer (U.S. Patent No. 5,610,163) in combination, is respectfully traversed.

The traversal of the rejection based on Nishimura and Banholzer from above is incorporated by reference here. The primary failing of the combination of Nishimura and Banholzer is the failure to suggest the specific combination of specific components: 1) the tiotropium compound, 2) the ciclesonide compound, and 3) the glucose, arabinose, lactose, saccharose or maltose excipient. Additionally, the combination of Nishimura and Banholzer fails to provide any hint to the unexpected synergistically advantageous properties of the combination specifically of the tiotropium and ciclesonide components.

Keller fails to provide any teachings which make up for the deficiencies of the Nishimura and Banholzer references. Keller discloses adding magnesium stearate to powder formulations to improve their moisture resistance; see, e.g., col. 4, lines 16-25. Keller teaches that its invention can be applied to powders containing a wide variety of active agents and includes tiotropium and ciclesonide as examples of possible actives; see, e.g., col. 6, line 13, to col. 7, line 10. Keller also provides a general discussion of possible excipients which

include some of the ones listed in the current claims; see, e.g., col. 8, lines 1-16. However, Keller provides no suggestion to specifically combine tiotropium, ciclesonide and one of the specific excipients recited in the current claims. Further, Keller certainly provides no hint that such a combination would provide unexpected synergistically advantageous properties, as shown by applicants.

Accordingly, the combination of Keller, Nishimura and Banholzer is equally insufficient in supporting the nonobviousness of the claimed invention as the combination of Nishimura and Banholzer is. This rejection under 35 U.S.C. §103 should, thus, also be withdrawn.

It is submitted that the claims are in condition for allowance. However, the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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Attorney Docket No.: 01-1174-1-C1

Date: September 23, 2009

JAS/dp